Remarks

This Preliminary Amendment is submitted with a Request for Continued Examination. Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 61-120 are pending in the application, with claims 61 and 90 being the independent claims. Claims 28-60 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 61-120 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Support for new claims 61-120 can be found throughout the specification and examples. Specific support can be found, *inter alia*, as follows:

parallel screening method	page 4, lines 4-8; page 5, lines 28-36; page 6, lines 11-17; Examples
test cells of the same type	page 8, lines 4-9; Examples
different target molecules	page 4, lines 24-26; page 10, lines 9-17; Examples
"wherein said biological activities . . . "	page 8, lines 27-page 9, line 28; page 11, lines 35-page 13, line 27; Examples
metabolic-coupled signal transduction; Ras, Raf, Bcl-2	page 9, lines 9-13; page 20, lines 19-page 22, line 24; Example 1
receptor-coupled signal transduction; "target molecules include receptor tyrosine kinases . . ."; "target molecules include EGF . . ."	page 9, lines 9-28; page 17, line 24-page 20, line 22; Examples
"said biological activity is one or more pathological effects."; "said biological activity is either proliferation or apoptosis or a combination thereof."	page 8, lines 28-31; page12, line 32-page 14, line 4; page 16, line 26-page 17, line 5; Examples

"test cells are transformed with DNA . . ."	page 7, lines 1-9; page 10, lines 9-17; page 10, lines 19-24; page 17, line 24-page 18, line 2; Examples
detection systems	page 13, line 13-page 17, line 5; Examples
test cells origins	page 6, lines 30-32; page 8, lines 4-12; Examples
test cells of different types or of the same type but with a different state of differentiation or activation	page 8, lines 14-25; page 10, lines 19-31

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Summary of the Invention

To remind the Examiner, the main feature of the claimed invention is that that the same test substance can be applied to a number of different cellular substrates in one operation, allowing for an efficient, high throughput assay for screening the effect of a substance on the function, such as signal transduction, of the target molecules in living cells. Different detection systems can be used to investigate the effect of the test substance on different regulatory mechanisms of the same target molecule. This high throughput parallel screen of the effects of a test substance on the biological activities of the target molecule in cells is novel, as discussed below.

Rejections under 35 U.S.C. § 103

In re Vaeck (947F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)), outlines the factors required for establishing a *prima facie* case for obviousness: prior art references that teach all claim limitations, a motivation to combine the references in the references themselves or knowledge known to a person of skill in the art at the time the invention was made, and a reasonable expectation of success from the combination elements in the references. As discussed below, Applicants respectfully assert that these requirements have not been met to support any *prima facie* argument for obviousness for the new claims.

Foulkes *et al.* in view of Fodor *et al.*

Claims 28-44, 46, 49-51, 53, 55-56 and 58-60 were rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Foulkes *et al.* in view of Fodor *et al.* Specifically, the Examiner broadly asserted that the assay of Foulkes *et al.* meets most of the limitations of the claims, while Fodor *et al.* provides the limitation of the target molecule being a receptor protein. Applicants respectfully traverse this rejection as it may apply to the new claims.

The cited references do not contain every limitation of the claims.

Foulkes *et al.* describes a screening method for identifying molecules "capable of transcriptionally modulating one or more genes encoding growth factors or receptors". Foulkes *et al.*, page 21, lines 15-16. Every example, claim and embodiment in Foulkes *et al.* refers to transcriptional modulation of the target molecule. Nowhere does Foulkes *et*

al. teach measuring the effect of the substance on the biological activity of a target molecule using a detection system, wherein the biological activity is selected from the group consisting of metabolic-coupled signal transduction, receptor-coupled signal transduction, and a pathological effect.

Transcription and biological activities are two very different characteristics of a protein. Transcriptional assays are solely based on measuring the rate of mRNA synthesis for a target. The assay of Foulkes *et al.* does not even require the presence of the target protein in the cell, as it is only dependent on the transcriptional regulatory mechanisms of the protein, such as the promoter. The biological activity of the target protein is never a part of the assay. In contrast, the claimed invention is dependent on not only the presence of the target protein, but its biological function. This distinction yields different assays based on very different principles. Foulkes *et al.* cannot disclose the assay of the claimed invention.

The Examiner makes the argument that Foulkes *et al.* "teaches the detection of an agent that up regulates and down regulates receptor protein, which indirectly and inherently affects the activity of a biological target molecule," (page 12, Office Action). Applicants respectfully disagree, as it is well known in the art that transcription levels do not necessarily control the activity of a protein. Many other quantitative physical factors affect the activity, such as translational levels, post-translational processing, protein turnover, etc., as well as such regulatory mechanisms as phosphorylation. Even without nascent transcription, the target protein can remain active for a lengthy period of time, which would give false readings in such an assay. Likewise, increases in transcription may not increase protein activity as the transcript may not be properly processed, or the

protein may be bound to an inhibitor (*e.g.* NF-κB and IκB complexes). Thus, affecting transcription of a protein does not necessarily affect its activity.

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). "Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3rd 743, 745, 49 USPQ2d 1949, 1950-1 (Fed. Cir. 1999). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). All foregoing citations are as found on page 2100-52 of M.P.E.P., 8th ed. (rev. February 2003).

Because transcription *may or may not* influence the biological activity of a protein, it is not an inherent trait that may be used to support a rejection of obviousness. Foulkes *et al.* does not teach the use of the biological activities of the claimed invention, instead using a different mechanism altogether. Since Foulkes *et al.* does not teach the use of the biological activities of the target protein in the claimed invention, and cannot rely upon inherency to remedy this deficiency, Foulkes *et al.* cannot meet the limitations of the claims as required to support a *prima facie* case for obviousness.

With respect to transcription-based assays within the scope of the claimed invention, Applicants draw the Examiner's attention to the fact that the inducible promoters of the instant invention are not the transcription regulatory elements of the

target protein. Instead, these constructs use promoters that are not the distinguishing factor between the cells. Example 2 uses the same inducible promoter construct for both targets, EGF and HGF. The specificity is determined by which target protein (HGF or EGF) is affected by the test substance, and is dependent on the biological activity of the target protein, not on the promoter. *See* page 10, lines 9-17 of the specification.

Fodor *et al.* does not remedy the deficiencies of Foulkes *et al.*, as it also teaches an assay based on entirely different principles than the claimed invention. Whereas the claimed invention requires biological activity of the target protein, the assay of Fodor *et al.* precludes biological activity, as the target molecules are fixed in array of molecules bound to a solid surface. In no way can the bound target molecules display any of the biological activities of the claimed invention. Therefore, Foulkes *et al.* in view of Fodor *et al.* do not teach each and every limitation of the claims and thus do not provide a proper *prima facie* case for obviousness.

There is no motivation to combine

A person of skill in the art would have no motivation to combine the cited references as neither reference contain any suggestion to do so. The assays of the references are very different and lead to different results. The assay of Foulkes *et al.* is a cell-based assay that screens for gene transcription inhibitors. The assay of Fodor *et al.* is a fixed array-based assay that screens for direct binding of biomolecules, primarily polynucleotides. There is no motivation in either reference to combine elements of the array-based assay with cell-based assay. The Examiner argued that the "marker" genes of column 5, lines 44-62 of Fodor *et al.* would be desirable to use in the screen of

Foulkes *et al.* (Office Action, page 5). However, Fodor *et al.* only describes these marker genes as being useful for monitoring gene expression patterns associated with cancer etiology, as an important embodiment of Fodor *et al.* is to monitor gene expression, in human, viral, and bacterial samples (column 5, lines 34-36 and 59-62, Fodor *et al.*). Fodor *et al.* does not describe the promoter regions and other transcription regulatory elements of these "marker" genes that are the actual targets of Foulkes *et al.* No where does Fodor *et al.* suggest the desirability to use these marker genes to screen test substances in a cell-based assay of Foulkes *et al.* or the claimed invention. Therefore, Applicants assert there is no motivation to combine the cited references.

There is no expectation of success.

Assuming *arguendo* that a person of skill in the art would attempt to combine elements of Foulkes *et al.* with Fodor *et al.*, there is no expectation of success as the two teach methods that are very different and not easily combinable. Even at the most basic level, the genes of Fodor *et al.* are not directly transferrable to Foulkes *et al.* because Foulkes *et al.* requires the regulatory regions of the target genes. Fodor *et al.* does not describe the regulatory sequences for gene expression for any of the "marker" genes pointed out by the Examiner. Instead, Fodor *et al.* teaches that to monitor gene expression, the preferred target is cDNA reverse transcribed from mRNA (column 18, lines 52-64, Fodor *et al.*). mRNA does not normally contain all the necessary transcription regulatory sequences, so cDNA reverse transcribed from it would be unsuitable for use in the assay of Foulkes *et al.* Clearly, a person of skill in the art would have no expectation of success to combine the teachings of the cited references.

As discussed *supra*, Foulkes *et al.* and Fodor *et al.*, when combined, do not teach each and every element of the claimed invention. There is no motivation to combine these references, and even if combined, there is no expectation for success. As there is no possibility of this combination of references arriving at the claimed invention, Applicants assert that no *prima facie* case for obviousness has been established. Therefore, Applicants respectfully request that the rejection be withdrawn.

Foulkes *et al.* in view of Fodor *et al.* in further view of Chapman *et al.*

Claim 57 was rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Foulkes *et al.* in view of Fodor *et al.* in further view of Chapman *et al.* Specifically, the Examiner added the GFP of Chapman *et al.* to the rejection discussed *supra.* Applicants respectfully traverse that rejection as it may apply to the amended claims.

As outlined above, Applicants assert that the combination of Foulkes *et al.* and Fodor *et al.* do not arrive at the invention of the amended claims as they do not teach alone or in combination a parallel screening method for measuring the effect of the substance on the biological activity of a target molecule using a detection system, wherein the biological activity is selected from the group consisting of metabolic-coupled signal transduction, receptor-coupled signal transduction, and a pathological effect. Chapman *et al.* does not remedy these deficiencies as it is drawn to a method of producing a chimeric peptide, such as an antibiotic peptide (column 1, lines 6-8, Chapman *et. al.*). In the Examples and Figures the Examiner cited on page 6 in the outstanding Office Action, GFP is expressed as a fusion with a viral protein. In both cases, the marker is used to measure protein production after recombinant viral

transduction. GFP is not used in a screening method, is used only in the context of a fusion with the protein of interest, and is never described for use as an independent marker protein. Indeed, a major advantage cited for its use in Chapman *et al.* is its ability to maintain its fluorescence in a fusion protein (Chapman *et al.* column 8, lines 5-8). Therefore, this reference cannot teach a method for screening for molecules that affect the biological activity of target molecules, as required by the claimed invention.

There is no motivation to combine the fusion GFP protein of Chapman *et al.* with the other references as in neither reference is there any suggestion that a fusion of GFP with the target protein as described in Chapman *et al.* would be desirable since Foulkes *et al.* requires the promoter region for the target protein, and Fodor *et al.* does not describe using a reporter protein for its assay. There is also no expectation of success that this fusion protein would succeed in these assays since Fodor *et al.* relies on detection molecules conjugated to the molecules (Fodor *et al.* column 81, "Labeling Techniques"), and Foulkes *et al.* requires the transcription regulatory regions for its assay. Therefore, Applicants assert that a *prima facie* case has not been established, and respectfully request that the rejection be withdrawn.

Foulkes *et al.* in view of Fodor *et al.* in further view of Bilodeau *et al.*

Claim 45 was rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Foulkes *et al.* in view of Fodor *et al.* in further view of Bilodeau *et al.* Specifically, the Examiner added the KDR of Bilodeau *et al.* to the rejection discussed *supra.* Applicants respectfully traverse that rejection as it may apply to the amended claims.

As outlined above, Applicants assert that the combination of Foulkes *et al.* and Fodor *et al.* do not arrive at the invention of the amended claims as they do not teach a parallel screening method for measuring the effect of a substance on the biological activity of a target molecule in using a detection system, wherein the biological activity is selected from the group consisting of metabolic-coupled signal transduction, receptor-coupled signal transduction, and a pathological effect. Bilodeau *et al.* does not remedy these deficiencies as it is drawn to a particular family of pharmaceutical compounds and testing thereof and does not describe any parallel screening method. A person of skill in the art would have no motivation to combine the KDR of Bilodeau *et al.* with the assays of Foulkes *et al.* in view of Fodor *et al.*, as there is no suggestion indicating the desirability to use KDR in an assay as described in those references. Further, there is no expectation of success as Bilodeau *et al.* does not disclose the transcription regulatory regions of KDR, as required by Foulkes *et al.*, or any sequence information. Therefore, Applicants assert that a *prima facie* case has not been established, and respectfully request that the rejection be withdrawn.

Foulkes *et al.* in view of Fodor *et al.* in further view of Nishi *et al.*

Claim 45 was rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Foulkes *et al.* in view of Fodor *et al.* in further view of Nishi *et al.* Specifically, the Examiner added the neurokinin receptor of Nishi *et al.* to the rejection discussed *supra.* Applicants respectfully traverse that rejection as it may apply to the amended claims.

As outlined above, Applicants assert that the combination of Foulkes *et al.* and Fodor *et al.* do not arrive at the invention of the amended claims as they do not teach

alone or in combination parallel screening method for measuring the effect of a substance on the biological activity of a target molecule in using a detection system, wherein the biological activity is selected from the group consisting of metabolic-coupled signal transduction, receptor-coupled signal transduction, and a pathological effect. Nishi *et al.* does not remedy these deficiencies as it is drawn to a particular family of pharmaceutical compounds and testing thereof and does not describe any parallel screening method. A person of skill in the art would have no motivation to combine the neurokinin receptor of Nishi *et al.* with the assays of Foulkes *et al.* in view of Fodor *et al.*, as there is no suggestion indicating the desirability to use that receptor in an assay as described in those references. Further, there is no expectation of success as Nishi *et al.* does not disclose the transcription regulatory regions of the neurokinin receptor, as required by Foulkes *et al.*, or any sequence information. Therefore, Applicants assert that a *prima facie* case has not been established, and respectfully request that the rejection be withdrawn.

Foulkes *et al.* in view of Fodor *et al.* in further view of Gerald *et al.*

Claim 45 was rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Foulkes *et al.* in view of Fodor *et al.* in further view of Gerald *et al.* Specifically, the Examiner added the serotonin receptor of Gerald *et al.* to the rejection discussed *supra.* Applicants respectfully traverse that rejection as it may apply to the amended claims.

As outlined above, Applicants assert that the combination of Foulkes *et al.* and Fodor *et al.* do not arrive at the invention of the amended claims as they do not teach

alone or in combination a parallel screening method for measuring the effect of the substance on the biological activity of a target molecule using a detection system, wherein the biological activity is selected from the group consisting of metabolic-coupled signal transduction, receptor-coupled signal transduction, and a pathological effect. Gerald *et al.* does not remedy these deficiencies as it is directed to the characterization of a particular receptor and does not teach any parallel screening method. A person of skill in the art would have no motivation to combine the 5-HT_4 of Gerald *et al.* with the assays of Foulkes *et al.* in view of Fodor *et al.*, as there is no suggestion indicating the desirability to use 5-HT_4 in an assay as described in those references. Further, there is no expectation of success as Gerald *et al.* as there is no guidance for elucidating the transcriptional control regions of the receptor gene, as required by Foulkes *et al.* The sequences provided that mention untranslated sequences are described as having only partial sequences (see Gerald *et al.*, column 4, lines 38-45). Therefore, Applicants assert that a *prima facie* case has not been established, and respectfully request that the rejection be withdrawn.

Foulkes *et al.* in view of Fodor *et al.* in further view of Johnson *et al.*

Claim 45 was rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Foulkes *et al.* in view of Fodor *et al.* in further view of Johnson *et al.* Specifically, the Examiner added the Raf receptor of Johnson *et al.* to the rejection discussed *supra.* Applicants respectfully traverse that rejection as it may apply to the amended claims.

As outlined above, Applicants assert that the combination of Foulkes *et al.* and Fodor *et al.* do not arrive at the invention of the amended claims as they do not teach

alone or in combination measuring the effect of the substance on the biological activity of a target molecule using a detection system, wherein the biological activity is selected from the group consisting of metabolic-coupled signal transduction, receptor-coupled signal transduction, and a pathological effect. Johnson *et al.* does not remedy these deficiencies as it is directed to MEKK proteins and does not disclose a parallel screen. A person of skill in the art would have no motivation to combine the Raf of Johnson *et al.* with the assays of Foulkes *et al.* in view of Fodor *et al.*, as there is no suggestion to do so. Specifically, Foulkes *et al.* is directed to modulating the transcription of growth factors and their receptors, and Raf is not a growth factor, but a kinase downstream of receptor activation (Johnson, *et al*, column 2, lines 5-10). Further, there is no expectation of success as Johnson *et al.* as there is no guidance for elucidating the transcriptional control regions of the Raf gene, as required by Foulkes *et al.* Therefore, Applicants assert that a *prima facie* case has not been established, and respectfully request that the rejection be withdrawn.

Other Matters

Applicants note that the Examiner has withdrawn the rejection of claim 54, drawn to the use of bcl-2 as the target molecule, and instead objected to it on the basis of being dependent on a rejected claim. Claim 54 has been cancelled, but new claims 65 and 94 are also drawn to the use of bcl-2 as the target molecule.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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